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# HEMORRHAGIC FEVER WITH RENAL SYNDROME (KOREAN HEMORRHAGIC FEVER)

ANNUAL SUMMARY REPORT

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July 31, 1989

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012



Grant No. DAMD17-86-G-6011

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Chongnoku, Seoul 110-702, Korea

SECURITY CLASSIFICATION OF THIS PAGE

# REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

| | |
|---|---|
| 1a. REPORT SECURITY CLASSIFICATION: Unclassified | 1b. RESTRICTIVE MARKINGS |
| 2a. SECURITY CLASSIFICATION AUTHORITY | 3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; Distribution unlimited |
| 2b. DECLASSIFICATION/DOWNGRADING SCHEDULE | |
| 4. PERFORMING ORGANIZATION REPORT NUMBER(S): HFRS-2 | 5. MONITORING ORGANIZATION REPORT NUMBER(S) |
| 6a. NAME OF PERFORMING ORGANIZATION: Korea University College of Medicine; 6b. OFFICE SYMBOL (If applicable) | 7a. NAME OF MONITORING ORGANIZATION |
| 6c. ADDRESS (City, State, and ZIP Code): 4, 2nd Street Myungyundong Chongnoku, Seoul 110-702, Korea. | 7b. ADDRESS (City, State, and ZIP Code) |
| 8a. NAME OF FUNDING/SPONSORING ORGANIZATION: US Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable) | 9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-86-G-6011 |
| 8c. ADDRESS (City, State, and ZIP Code): Fort Detrick Frederick, MD 21701-5012 | 10. SOURCE OF FUNDING NUMBERS |

| PROGRAM ELEMENT NO. | PROJECT NO. | TASK NO. | WORK UNIT ACCESSION NO. |
|---|---|---|---|
| 62770A | 3M1-62770A071 | AB | 381 |

11. TITLE (Include Security Classification)

HEMORRHAGIC FEVER WITH RENAL SYNDROME (KOREAN HEMORRHAGIC FEVER)

12. PERSONAL AUTHOR(S): Lee Ho Wang

| 13a. TYPE OF REPORT | 13b. TIME COVERED | 14. DATE OF REPORT (Year, Month, Day) | 15. PAGE COUNT |
|---|---|---|---|
| Annual | FROM 88/2/10 TO 89/2/9 | 89/7/31 | |

16. SUPPLEMENTARY NOTATION

| 17. COSATI CODES | | | 18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number) |
|---|---|---|---|
| FIELD | GROUP | SUB-GROUP | |
| 06 | 03 | | Hantavirus; Hantaan virus; Seoul virus; Puumala virus; scrub typhus; murine typhus; spotted fever; seroepidemiology; IFA; Elisa; PRNT; RA I; (RT) |
| 06 | 13 | | |

19. ABSTRACT (Continue on reverse if necessary and identify by block number)


Hantavirus is ubiquitous in the world and the total number of reported HFRS patient in Euro-Asia is about 200,000 with 5-7% mortality annually. Hemorrhagic fever with renal syndrome (HFRS) is an important military problem since large epidemics of HFRS occurred among soldiers in many past wars and although predominantly associated with field mice in rural areas, it is now being recognized that urban rats and laboratory rats are also reservoirs of HFRS in many parts of the world.

Therefore, global surveys of the distribution of hantaviruses and surveillance of HFRS are important for prevention of this highly fatal disease. It is also important to investigate antigenic differences of strains of Hantavirus isolated from rodents caught in non-endemic areas of the world because HFRS patients have never been documented in many areas despite the finding of positive rodents there.


| 20. DISTRIBUTION/AVAILABILITY OF ABSTRACT | 21. ABSTRACT SECURITY CLASSIFICATION | |
|---|---|---|
| ☑ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS | Unclassified | |
| 22a. NAME OF RESPONSIBLE INDIVIDUAL: Virginia Miller | 22b. TELEPHONE (Include Area Code): 301/663-7325 | 22c. OFFICE SYMBOL: SGRD-RMI-S |

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

The methods for diagnosis of HFRS, isolation of hantaviruses from man and rodents are discribed previously.

There were 367 cases of HFRS in Korea in 1988 and recently the no. of HFRS patients are increasing in urban cities, and large epidemics of scrub typhus and murine typhus occurred before and during the epidemic season of HFRS. Many Siberian tick typhus patients were confirmed serologically among suspect HFRS in Korea for the first time. Six strains of Hantaan virus were also isolated from Apodemus agrarius captured in Kyungsangbukdo, Korea where HFRS was not reported previously.

In a global survey of HFRS, Hantavirus infection was demonstrated in Sri Lanka and one strain of Seoul virus-like virus was isolated from a wild house rat caught in Colombo. Four HFRS patients were documented serologically and clinically in Sri Lanka and they were misdiagnosed as leptospirosis, hepatitis and meningitis.

## SUMMARY

There were 367 cases of hospitalized HFRS patients serologically confirmed at our laboratory and 97 and 6 of them were ROK Army and US Army soldiers, respectively in Korea during 1988. Epidemics of scrub typhus and murine typhus occurred about a month before and during the epidemic season of HFRS and many cases of spotted fever patients were diagnosed at our laboratory among 1,389 suspect HFRS in 1988 for the first time.

Six strains of Hantaan virus were isolated from Apodemus agrarius cought in Yechun, Kyungsangbukdo, Korea where HFRS had not been reported previously and one strain of Seoul virus from R. norvegicus caught in Kunsan city.

As a part of a global survey of HFRS, Hantavirus infection was demonstrated for the first time in Sri Lanka.

A strain of Seoul virus was isolated from R. norvegicus caught in the Colombo harbour. Four HFRS patients were documented serologically and clinically in Sri Lanka for the first time. They had been misdiagnosed clinically as leptospirosis, hepatitis and meningitis. An HFRS patient had meningoencephalitis symptoms that were completely different from known clinical symptoms of HFRS in the endemic areas. Therefore, it could be speculated that clinical features of HFRS patients infected with Hantaviruses in tropic areas where this disease is not known to exist may be more diverse than the classic forms of HFRS in the endemic areas.


## FOREWORD

In conducting the research described in this report, the investigators (s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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## INTRODUCTION

During the Korean War more than 3,200 United Nations troops in Korea developed a rare hemorrhagic fever, a situation that attracted worldwide attention (1). Since then it has been known as Korean hemorrhagic fever (KHF) in Korea. This disease was an important military problem because large epidemics occurred among soldiers during several wars. More than 12,600 cases of epidemic hemorrhagic fever (EHF) occurred among one million Japanese soldiers in Manchuria (2) and several hundred cases among Russian soldiers in the Far East (3) during World War II. Several thousand cases of war nephritis, clinically similar to Nephropathia epidemica (NE), were reported among British soldiers stationed in Flanders during World War I (4), and about 16,000 cases of NE occurred among German soldiers in Lapland and prisoners in Yugoslavia during World War II (5). About 14,000 cases of war nephritis clinically similar to NE were described among Northern Armies in the American Civil War (6).

In South Korea, 500 to 900 persons are hospitalized annually with this disease and about one third of these are soldiers (7). There were about 114,000 cases of HFRS in China in 1986 with 7% mortality, and several hundred cases of HFRS occurred in other countries of Asia and Europe (8,9).

The causative agent of KHF was first discovered in 1976 from Apodemus mice (10) and isolated from KHF patients in 1978 (11). This agent has been propagated in a human cell culture line (12), and it was named Hantaan virus after the Hantaan river which runs along the 38th Parallel between South and North Korea (13). Antigenic features, genetic properties and EM studies indicate that Hantavirus is a new genus of Bunyaviridae (14-17). A close etiological relationship has been established between KHF and HFRS in the USSR, NE in Scandinavia, and EHF in Eastern Europe, Japan and China (11, 18-21).

The working group on HFRS at a WHO meeting in Tokyo, 1982 recommended that all of the above diseases with different names should be referred to as "Haemorrhagic Fever with Renal Syndrome (HFRS)"(22). Recent seroepidemiologic surveys established that Hantaviruses are widely distributed throughout the world. Antibodies against Hantaan virus in human sera were demonstrated in India, Thailand, Iran, Greece, the U.S., Canada, Bolivia, Brazil, Gabon and Republic of Central Africa (23-26) and more recently in Taiwan, the Philippines, Malaysia, Singapore, Hong Kong, Fiji, Hawaii, Argentine, Uruguay and Paraguay (9,27).

Intraspecific transmission of Hantaan virus in Apodemus mice (28) has also been shown. Infection occurred among cage-mates up to 360 days after exposure, while large amounts of virus were excreted in urine and saliva. No evidence for the participation of ectoparasites in virus transmission was found. Infection with Hantaan virus is thought to be silent in animals (29), but is

associated with diverse clinical symptoms in human (30). A severe form is common in East Asia, while most European cases are mild (31). The disease is most often sporadic, but under special circumstances epidemics occur. Although predominantly associated with rural areas, HFRS is now being recognized as an urban problem in some countries (32,33) and a particular hazard to laboratory staff using rodents for biomedical research (9,34, 35). From 1975 to 1986, about 160 cases of HFRS. of which one was fatal, occurred in 34 animal rooms of research Institutes in Korea, Japan and Europe among personnel of the animal rooms as a result of exposure to infected rat colonies. Seventy-one % of Korea rats and 40% of the Japanese rats had antibodies to Hantaan virus. Commercial rabbits bought from breeding firms in Korea and Japan were seropositive to Hantaan virus and serum antibodies were found in 3.5% of 792 New Zealand rabbits (36). We have registered a Hantaan related virus isolated from an urban rat caught in Seoul, 1980 as Seoul virus in 1985 (37). Several strains of Seoul virus were isolated from urban rats caught in Korea and Japan (38) and many strains of Hantaan and Seoul virus were isolated from blood of HFRS patients in Vero E6 cell cultures (39).

Recently, there have been several outbreaks of acute hemorrhagic diseases among soldiers and farmers before and during the epidemic season of HFRS in Korea and it was confirmed that leptospirosis, scrub typhus and other rickettsiosis are the hemorrhagic diseases existing in Korea (40).

There are still many problems to be answered in research work of HFRS and some important issues are: a) global survey of Hantavirus infection and HFRS b) serologic identification of new hantaviruses isolated from the different parts of the world c) an animal model mimic to man d) pathogenesis of hemorrhages and nephritis and e) therapeutic agents and vaccines. This report describes 1) seroepidemiologic surveys of HFRS and other hemorrhagic diseases clinically similar to HFRS in Korea 2) demonstration of Siberian tick fever patient in Korea 3) presence of HFRS and isolation of a Hantavirus from an urban rat in Sri Lanka and 4) isolation of Hantavirus from a wild rodent caught in Chinhae, in southern part of South Korea.

## MATERIALS AND METHODS

### Survey areas

Survey areas for reservoir of HFRS and isolation of Hantaan and related agents from field mice, laboratory rats and urban rats were Wuncheon and Jinhae, S. Korea and Sri Lanka. Frozen lungs and sera from rodents from Sri Lanka were shipped in dry ice to Seoul by Air Flight.

Collection of field and urban rodents

Field and house rodents were captured by means of baited live traps and normal Apodemus mice were captured on Jeju island as described (11,14). Seronegative Apodemus mice and Wistar rats were used as sensitive detectors for Hantavirus isolation.

Processing rodents

Living rodents were identified and bled by cardiac puncture under chloroform anesthesia. Serum was separated for antibody titration. Necropsy tissue include lungs, spleen, liver, and kidneys. A portion of each organ was examined immediately by IFA for Hantavirus antigen and the remaining portion were frozen at -70 °C until processing for virus isolation.

Specimens from patients

Sera collected from suspected HFRS patients were used for serodiagnosis. Larger amounts of hyperimmune convalescent serum was collected from HFRS patients for experimental use.

Hantaviruses

All experimental and diagnostic work done with Vero E-6 and A549 cells infected with Hantaan virus, strains 76/118 and ROK83/109 isolated from patient bloods and adapted in Vero E-6 cells. To titrate the virus from rat lungs, 10% lung suspensions are prepared with BSS containing 0.2% bovine albumin clarified at 5,000 G for 20 min. at 4°C and supernatants are used as inoculum. The $ID_{50}$ of Hantaan virus strains 76/118 and 83/109 in Vero E6 cells was $10^{5.3}$, $10^{6.2}$ and $ID_{50}$ of Seoul virus strain 80/39 and Puumala virus strain Sotkamo in Vero E6 cells was $10^{5.8}$ and $10^{4.2}$/1.0 ml, respectively. All strains of hantaviruses are free from reovirus. It was proved by FA staining with polyvalent antireovirus immune sera.

Preparation of antisera

In addition to convalescent sera obtained from HFRS patients and antisera from naturally infected rats and mice, laboratory animals were used as a source of antibody. Sera from immunized rabbits and rats were employed.

Tissue culture cells

A549 (12) and Vero E6 cells (14) were grown as described previously and used for virus isolation, preparation of FA antigen and virus plaque assay.

Virus isolation

The details of techniques used for demonstration of Hantavirus antigen by IFAT and virus isolation from HFRS patients and animals in Vero E6 cell cultures and in animals have been described previously (11,31.33).

Demonstration of antigen and antibodies of HFRS by use of immunofluorescent antibody techniques (IFAT)

The techniques employed for demonstration of antibodies and antigens of Hantavirus in specimens from patients, rodents and other animals have been described in detail (11,33,36).

Plaque reduction neutralization test (PRNT)

Neutralizing antibody titers were determined by plaque reduction methods employing immunoperoxidase staining (41). Hantaan and Seoul virus plaques developed readily in 5 to 7 days but Puumala and Prospect Hill staining virus plaques developed in 7 to 10 days under 0.5% methycellulose. PRNT titers are expressed as the reciprocal of the highest dilution of serum resulting in 80% or greater reduction in the number of virus plaques.

ELISA test

This test for demonstration of IgG and IgM antibodies against Hantaan virus was developed at USAMRIID (31). However, it can not differentiate Hantaan virus infection from Seoul virus infection because of cross reaction between them and the method is as described (31).

Antibody test against rickettsiosis

R. tsutsugamushi, R. typhi and R. sibirica strains were obtained from US Army Medical Research Unit in Malaysia and antigens were prepared in Yolk according to the instruction. Micro-immunofluorescent technique were used for antibody titration.

## RESULTS

A. Seroepidemiological survey of HFRS and other hemorrhagic diseases among suspect HFRS patients in Korea in 1988.

1. Epidemiologic features of HFRS

There were 367 hospitalized cases of HFRS confirmed serologically at our Institute in 1988 and 6 of them were US Army soldiers as shown in Table 1. Total no. of serum from suspected HFRS in 1988 examined against Hantaan virus was 1,389 and only 26% of them were HFRS patients as shown in Table 2. The ratios of serologically confirmed HFRS patients among clinically suspected HFRS patients by civilian doctors and ROK Army and US Army doctors are about 22%, 56% and 11%, respectively as shown in Table 3. It is noteworthy that ratio of confirmed cases to suspected cases in 1980s is lower than that of 1970s because clinicians have sent us sera from only severe cases of suspect HFRS in 1970s because clinicians have sent us sera from only severe cases of suspect HFRS in 1970s while doctors are sending us more sera from mild suspected HFRS patients and other hemorrhagic fever patients in these years.

Clinicians have made better clinical diagnosis of HFRS during the epidemic season, October-January, than non-epidemic season of HFRS. Monthly occurrence of HFRS among civilians, ROK Army and US Army in 1988 is shown in Table 3. Patients occur throughout the year and there are two peaks, a small peak in May-August, and a large peak in October-January. One of the new epidemiologic features of HFRS in Korea is the increasing number of HFRS patients in urban areas of Seoul city as shown in Table 4. There were 92 cases of HFRS in Seoul in 1988. These patients were only hospitalized severe cases, and usually moderate and mild cases are not included because Seoul virus infection is mild and usually diagnosed clinically as influenza or unknown fever. HFRS cases occurred in all districts of Seoul as shown in Table 5. Male patients are the dominant group of HFRS as shown in Table 6 although 97 male soldier patients were not included in this no. of male cases. Table 4 shows the distribution of HFRS among civilians and about 80% of the patients were in Seoul, Kyunggido and Kangwondo, northern parts of South Korea. All of the 97 HFRS patients among Korean soldiers occurred in Kyunggido, Kangwondo and Seoul where main forces of Korean Army is stationed as shown in Table 7. All 6 HFRS patients among U.S. Army soldiers occurred in Kyunggido, where the 2nd Division of U.S. Army is stationed.

2. <u>Epidemic outbreak of acute febrile hemorrhagic diseases during the epidemic season of HFRS in 1988</u>.

As shown in Tables 2,8,13 and 14, the total no. of confirmed cases of scrub typhus was 114 among 1,389 suspected HFRS. These sera from the hospitalized patients were sent to our laboratory from hospitals in and nearby Seoul for serologic diagnosis of HFRS. The no. of scrub typhus patients among civilians, ROK Army and U.S. Army is 108, 6 and none respectively. almost all of the patients occurred in October and November, about a month before the large epidemic season of HFRS as shown in Table 8, and 13. Distribution of scrub typhus patients in South Korea is shown in Table 8 and large portion of the patients were confirmed in Kyunggido, Seoul city, Kangwon-do, and Kyungsangnam-do, and a few patients also occurred in other provinces as well. About 60% of scrub typhus patients among civilians were female and about 75% of the patients were in the age group of over 41 as shown in Table 6. A large outbreak of murine typhus was demonstrated for the first time in Korea in 1988 as shown in Tables 2,6,9 and 12. It is noteworthy that murine typhus occurred in every month of the year and large no. of the patients were distributed in Seoul, Kyunggi-do, Kangwon-do, Chung-

Table 1.
Hospitalized cases of Hemorrhagic fever with renal syndrome patients in the Republic of Korea.

| Year | Korean civilian | Korean soldiers | US soldiers | Total |
|---|---|---|---|---|
| 1951 | ... | 26 | 827 | 853 |
| 1952 | ... | 18 | 833 | 851 |
| 1953 | ... | ... | 455 | 455 |
| 1954 | 19 | ... | 307 | 326 |
| 1955 | ... | ... | 20 | 20 |
| 1956 | ... | 26 | 28 | 54 |
| 1957 | ... | 21 | 13 | 34 |
| 1958 | ... | 20 | 15 | 35 |
| 1959 | ... | 47 | 79 | 126 |
| 1960 | ... | 185 | 10 | 195 |
| 1961 | ... | 341 | 27 | 368 |
| 1962 | ... | 311 | 29 | 340 |
| 1963 | ... | 257 | 11 | 268 |
| 1964 | 18 | 205 | 22 | 245 |
| 1965 | 2 | 110 | 99 | 211 |
| 1966 | 11 | 82 | 36 | 129 |
| 1967 | 13 | 86 | 31 | 130 |
| 1968 | 26 | 102 | 28 | 156 |
| 1969 | 48 | 134 | 9 | 191 |
| 1970 | 131 | 221 | 13 | 365 |
| 1971 | 391 | 358 | 2 | 751 |
| 1972 | 186 | 203 | 0 | 389 |
| 1973 | 241 | 237 | 0 | 478 |
| 1974 | 176 | 251 | 0 | 427 |
| 1975 | 466 | 370 | 1 | 837 |
| 1976 | 585 | 304 | 4 | 893 |
| 1977 | 288 | 241 | 7 | 536 |
| 1978 | 207 | 168 | 10 | 385 |
| 1979 | 241 | 122 | 1 | 364 |
| 1980 | 185 | 72 | 1 | 258 |
| 1981 | 377 | 164 | 2 | 543 |
| 1982 | 378 | 123 | 3 | 504 |
| 1983 | 402 | 98 | 3 | 503 |
| 1984 | 568 | 156 | 6 | 730 |
| 1985 | 531 | 159 | 7 | 697 |
| 1986 | 530 | 166 | 14 | 710 |
| 1987 | 533 | 163 | 5 | 701 |
| 1988 | 264 | 97 | 6 | 367 |
| Total | 6,817 | 5,644 | 2,964 | 15,425 |

Numbers of patients since 1978 are serologically confirmed cases at The Institute for Viral Diseases, Korea University.

Table 2.
Number of HFRS, scrub typhus, murine typhus and spotted fever diagnosed serologically among clinically suspect HFRS patients at The Institute for Viral Diseases, Korea University in Korea, 1988.

| | | | |
|---|---|---|---|
| Total no. of HFRS / Total no. of serum tested | [1] | = | 361 / 1,389 (26%) |
| Total no. of scrub typhus / Total no. of serum tested | | = | 114 / 1,389 (8%) |
| Total no. of murine typhus / Total no. of serum tested | | = | 448 / 1,389 (32%) |
| Total no. of spotted fever / Total no. of serum tested | | = | 327 / 1,389 (24%) |
| Total no. of leptospirosis / Total no. of serum tested | | = | 37 / 1,389 (3%) |
| Total no. of unknown sera / Total no. of serum tested | | = | 102 / 1,389 (7%) |

[1] No. of confirmed patient serologically / No. of serum from suspect HFRS patient tested

Table 3.
Number of serologically confirmed cases of Hemorrhagic fever with renal syndrome patients at The Institute for Viral Diseasaes, Korea University in Korea in 1988.

| Month | No. of antibody positive sera against Hantaan virus / No. of tested sera from suspected patients | | | |
|---|---|---|---|---|
| | Civilian | ROK Army | US Army | Total |
| 1 | 27/91 | 2/8 | 0/3 | 29/102 |
| 2 | 11/72 | 2/5 | 0/0 | 13/77 |
| 3 | 7/62 | 1/6 | 0/6 | 8/74 |
| 4 | 4/54 | 1/5 | 0/4 | 5/63 |
| 5 | 19/86 | 3/13 | 0/2 | 22/101 |
| 6 | 17/83 | 4/13 | 0/5 | 21/101 |
| 7 | 20/85 | 1/7 | 0/2 | 21/94 |
| 8 | 11/67 | 4/14 | 0/2 | 15/83 |
| 9 | 3/84 | 1/5 | 0/1 | 4/90 |
| 10 | 20/169 | 14/20 | 2/9 | 36/198 |
| 11 | 88/257 | 53/60 | 3/12 | 144/329 |
| 12 | 37/106 | 11/17 | 1/9 | 49/132 |
| Total | 264/1,216 (22%) | 97/173 (56%) | 6/55 (11%) | 367/1,444 (26%) |

Table 4.
Distribution of confirmed cases of Hemorrhagic fever with renal syndrome patients among civilian in Korea in 1988 at The Institute for Viral Diseases, Korea University.

| Name of province | Month | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Seoul city | 10 | 5 | 5 | 2 | 13 | 5 | 11 | 6 | 2 | 10 | 18 | 5 | 92 |
| Kyounggi-do | 10 | 4 | 2 | 1 | 4 | 9 | 5 | 3 | 1 | 3 | 28 | 18 | 88 |
| Kangwon-do | 2 | 1 | 0 | 0 | 2 | 2 | 1 | 1 | 0 | 3 | 19 | 8 | 39 |
| Chungcheongbuk-do | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 2 | 2 | 2 | 9 |
| Chungcheongnam-do | 3 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 7 | 3 | 17 |
| Kyungsangbuk-do | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 4 |
| Kyungsangnam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 | 1 | 7 |
| Jeollabuk-do | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| Jeollanam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 6 |
| Total | 27 | 11 | 7 | 4 | 19 | 17 | 20 | 11 | 3 | 20 | 88 | 37 | 264 |

Table 5.
Distribution of HFRS patients in districts of Seoul city in 1988.

| Name of district | No. of patients | Name of district | No. of patients |
|---|---|---|---|
| Yongsan-ku | 9 | Joong-Ku | 3 |
| Seongbuk-ku | 8 | Jungryang-ku | 3 |
| Seongdong-ku | 8 | Kwanak-ku | 3 |
| Yeongdeungpo-ku | 8 | Songpa-ku | 3 |
| Dobong-ku | 7 | Eunpyung-ku | 2 |
| Dongdaemun-ku | 6 | Kangseo-ku | 2 |
| Kuro-ku | 6 | Mapo-ku | 2 |
| Chongro-ku | 5 | Seocho-ku | 2 |
| Dongzak-ku | 4 | Seodaemun-ku | 2 |
| Kangdong-ku | 4 | Kangnam-ku | 1 |
| Nowon-Ku | 4 | | |
| | | Total | 92 |

Table 6.
Age and sex distribution of HFRS, scrub tyhus, murine typhus, spotted fever and leptospirosis by sex among civilian in Korea in 1988.

| Age | HFRS | | | scrub typhus | | | murine typhus | | | spotted fever | | | leptospirosis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | total | M | F | total | M | F | total | M | F | total | M | F | total |
| 0-10 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 |
| 11-20 | 16 | 0 | 16 | 2 | 1 | 3 | 10 | 9 | 19 | 10 | 10 | 20 | 3 | 2 | 5 |
| 21-30 | 57 | 9 | 66 | 6 | 6 | 12 | 59 | 27 | 86 | 49 | 21 | 70 | 6 | 4 | 10 |
| 31-40 | 36 | 13 | 49 | 7 | 3 | 10 | 47 | 23 | 70 | 45 | 18 | 63 | 4 | 2 | 6 |
| 41-50 | 40 | 14 | 54 | 11 | 14 | 25 | 53 | 26 | 79 | 39 | 20 | 59 | 4 | 2 | 6 |
| 51-60 | 32 | 17 | 49 | 7 | 22 | 29 | 52 | 45 | 97 | 32 | 25 | 57 | 1 | 2 | 3 |
| >60 | 13 | 16 | 29 | 12 | 16 | 28 | 53 | 22 | 75 | 28 | 13 | 41 | 4 | 3 | 7 |
| Total | 195 | 69 | 264 | 46 | 62 | 108 | 274 | 153 | 427 | 203 | 108 | 311 | 22 | 15 | 37 |

Table 7.
Occurrence of HFRS patients among ROKA soldiers in different areas of Korea in 1988.

| Name of area | No. of patient | Name of area | No. of patient |
|---|---|---|---|
| Seoul city | 3 | Munsan | 1 |
| Kyunggido | | Osan | 1 |
| Paju | 26 | Wuncheon | 1 |
| Yeoncheon | 16 | Kangwondo | |
| Pocheon | 7 | Whacheon | 12 |
| Kimpo | 3 | Chulwon | 7 |
| Koyang | 2 | Yangku | 4 |
| Songchu | 2 | Inje | 3 |
| Yangju | 2 | Hongcheon | 1 |
| Bupyung | 1 | Koseong | 1 |
| Dongducheon | 1 | Sachangri | 1 |
| | | Total : 97 patients | |

Table 8.
Distribution of confirmed cases of scrub typhus among civilian in Korea in 1988 at The Institute for Viral Diseases, Korea University.

| Name of province | Month | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Seoul city | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 12 | 4 | 1 | 19 |
| Kyounggi-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 15 | 17 | 2 | 39 |
| Kangwon-do | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 2 | 0 | 18 |
| Chungcheongbuk-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 3 |
| Chungcheongnam-do | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 | 1 | 0 | 5 |
| Kyungsangbuk-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Kyungsangnam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 9 | 0 | 18 |
| Jeollabuk-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 3 |
| Jeollanam-do | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Total | 3 | 0 | 1 | 0 | 0 | 1 | 1 | 3 | 3 | 57 | 36 | 3 | 108 |

Table 9.
Distribution of confirmed cases of murine typhus among civilian in Korea in 1988 at The Institute for Viral Diseases, Korea University.

| Name of province | Month | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Seoul city | 15 | 19 | 17 | 5 | 17 | 20 | 17 | 11 | 8 | 28 | 18 | 4 | 179 |
| Kyounggi-do | 10 | 8 | 8 | 9 | 10 | 12 | 4 | 2 | 12 | 20 | 22 | 3 | 120 |
| Kangwon-do | 1 | 4 | 0 | 0 | 5 | 2 | 4 | 1 | 2 | 12 | 8 | 3 | 42 |
| Chungcheongbuk-do | 0 | 1 | 4 | 0 | 0 | 2 | 1 | 0 | 0 | 3 | 0 | 1 | 12 |
| Chungcheongnam-do | 2 | 3 | 1 | 1 | 1 | 3 | 1 | 0 | 0 | 4 | 10 | 3 | 29 |
| Kyungsangbuk-do | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 6 |
| Kyungsangnam-do | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 14 | 1 | 22 |
| Jeollabuk-do | 2 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 7 |
| Jeollanam-do | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 4 | 0 | 9 |
| Cheju | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Total | 35 | 36 | 30 | 16 | 36 | 39 | 28 | 16 | 23 | 75 | 78 | 15 | 427 |

Table 10.
Distribution of confirmed cases of spotted fever among civilian in Korea in 1988 at The Institute for Viral Diseases, Korea University.

| Name of province | Month | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Seoul city | 2 | 8 | 8 | 2 | 6 | 8 | 16 | 5 | 6 | 22 | 26 | 7 | 116 |
| Kyounggi-do | 6 | 3 | 2 | 6 | 5 | 5 | 5 | 1 | 8 | 17 | 37 | 1 | 96 |
| Kangwon-do | 0 | 1 | 0 | 0 | 2 | 0 | 1 | 1 | 1 | 6 | 24 | 2 | 38 |
| Chungcheongbuk-do | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| Chungcheongnam-do | 1 | 1 | 1 | 0 | 1 | 1 | 2 | 0 | 0 | 3 | 8 | 1 | 19 |
| Kyungsangbuk-do | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Kyungsangnam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 19 | 0 | 26 |
| Jeollabuk-do | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 3 |
| Jeollanam-do | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4 | 0 | 7 |
| Total | 11 | 15 | 12 | 8 | 16 | 15 | 24 | 8 | 16 | 56 | 119 | 11 | 311 |

Table 11.
Distribution of confirmed cases of leptospirosis among civilian in Korea in 1988 at The Institute for Viral Diseases, Korea University.

| Name of province | Month | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | |
| Seoul city | 1 | 0 | 1 | 1 | 0 | 1 | 2 | 2 | 3 | 5 | 0 | 3 | 19 |
| Kyounggi-do | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 3 | 1 | 13 |
| Kangwon-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Chungcheongbuk-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| Chungcheongnam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Kyungsangbuk-do | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Kyungsangnam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jeollabuk-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Jeollanam-do | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 3 | 1 | 2 | 2 | 1 | 3 | 2 | 3 | 6 | 6 | 3 | 5 | 37 |

Table 12.
No. of confirmed hospitalized cases of HFRS, scrub typhus, murine typhus, spotted fever and leptospirosis by sex among civilian in 1988 in Korea.

| Month | HFRS | | | scrub typhus | | | murine typhus | | | spotted fever | | | leptospirosis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | total | M | F | total | M | F | total | M | F | total | M | F | total |
| 1 | 23/61 ψ | 4/30 | 27/91 | 1/61 | 2/30 | 3/91 | 26/61 | 9/30 | 35/91 | 8/61 | 3/30 | 11/91 | 1/61 | 2/30 | 3/91 |
| 2 | 7/44 | 4/28 | 11/72 | 0/44 | 0/28 | 0/72 | 26/44 | 10/28 | 36/72 | 10/44 | 5/28 | 15/72 | 0/44 | 1/28 | 1/72 |
| 3 | 7/42 | 0/20 | 7/62 | 0/42 | 1/20 | 1/62 | 21/42 | 9/20 | 30/62 | 10/42 | 2/20 | 12/62 | 1/42 | 1/20 | 2/62 |
| 4 | 4/35 | 0/19 | 4/54 | 0/35 | 0/19 | 0/54 | 10/35 | 6/19 | 16/54 | 6/35 | 2/19 | 8/54 | 2/35 | 0/19 | 2/54 |
| 5 | 11/50 | 8/36 | 19/86 | 0/50 | 0/36 | 0/86 | 24/12 | 12/36 | 36/86 | 9/50 | 7/36 | 16/86 | 0/50 | 1/36 | 1/86 |
| 6 | 14/59 | 3/24 | 17/83 | 1/59 | 0/24 | 1/83 | 21/59 | 18/24 | 39/83 | 13/59 | 2/24 | 15/83 | 3/59 | 0/24 | 3/83 |
| 7 | 15/46 | 5/39 | 20/85 | 0/46 | 1/39 | 1/85 | 15/46 | 13/39 | 28/85 | 13/46 | 11/39 | 24/85 | 1/46 | 1/39 | 2/85 |
| 8 | 9/42 | 2/25 | 11/67 | 2/42 | 1/25 | 3/67 | 9/42 | 7/25 | 16/67 | 5/42 | 3/25 | 8/67 | 3/42 | 0/25 | 3/67 |
| 9 | 1/51 | 2/33 | 3/84 | 1/51 | 2/33 | 3/84 | 13/51 | 10/33 | 23/84 | 8/51 | 8/33 | 16/84 | 5/51 | 1/33 | 6/84 |
| 10 | 11/76 | 9/93 | 20/169 | 25/76 | 34/93 | 55/169 | 47/76 | 28/93 | 75/169 | 30/76 | 26/93 | 56/169 | 4/76 | 2/93 | 6/169 |
| 11 | 64/144 | 24/113 | 88/257 | 14/144 | 20/113 | 34/257 | 50/144 | 28/113 | 78/257 | 85/144 | 34/113 | 119/257 | 0/144 | 3/113 | 3/257 |
| 12 | 29/63 | 8/43 | 37/106 | 2/63 | 1/43 | 3/106 | 12/63 | 3/43 | 15/106 | 6/63 | 5/43 | 11/106 | 2/63 | 3/43 | 5/106 |
| Total | 195/713 (27%) | 69/503 (14%) | 264/1216 (22%) | 46/713 (6%) | 62/503 (12%) | 108/1216 (9%) | 274/713 (38%) | 153/503 (30%) | 427/1216 (35%) | 203/713 (28%) | 108/503 (21%) | 311/1216 (26%) | 22/713 (3%) | 15/503 (3%) | 37/1216 (3%) |

ψ No. of serologically confirmed patient / No. of suspected patient tested

Table 13.
Number of HFRS, scrub typhus, murine typhus and spotted fever diagnosed serologically among clinically suspect HFRS patients in ROK soldiers at The Institute for Viral Diseases, Korea University in Korea, 1988.

| | | | |
|---|---|---|---|
| Total no. of HFRS | √ | 97 | |
| Total no. of serum tested | = | 173 | (56%) |
| Total no. of scrub typhus | | 6 | |
| Total no. of serum tested | = | 173 | (3%) |
| Total no. of murine typhus | | 21 | |
| Total no. of serum tested | = | 173 | (12%) |
| Total no. of spotted fever | | 16 | |
| Total no. of serum tested | = | 173 | (9%) |
| Total no. of leptospirosis | | 3 | |
| Total no. of serum tested | = | 173 | (2%) |
| Total no. of unknown sera | | 30 | |
| Total no. of serum tested | = | 173 | (17%) |

√ No. of confirmed patient serologically / No. of serum from suspect HFRS patient tested

Table 14.
Number of confirmed hospitalized cases of HFRS, scrub typhus, murine typhus, spotted fever and leptospirosis by month among ROK soldiers at The Institute for Viral Diseases, Korea University in Korea, 1988.

| Month | HFRS | scrub typhus | murine typhus | spotted fever | leptospirosis |
|---|---|---|---|---|---|
| 1 | 2/8 | 0/8 | 1/8 | 1/8 | 0/8 |
| 2 | 2/5 | 0/5 | 0/5 | 1/5 | 0/5 |
| 3 | 1/6 | 0/6 | 2/6 | 3/6 | 0/6 |
| 4 | 1/5 | 0/5 | 0/5 | 0/5 | 0/5 |
| 5 | 3/13 | 1/13 | 3/13 | 4/13 | 1/13 |
| 6 | 4/13 | 0/13 | 0/13 | 1/13 | 2/13 |
| 7 | 1/7 | 0/7 | 2/7 | 0/7 | 0/7 |
| 8 | 4/14 | 0/14 | 2/14 | 1/14 | 0/14 |
| 9 | 1/5 | 1/5 | 1/5 | 1/5 | 0/5 |
| 10 | 14/20 | 3/20 | 3/20 | 1/20 | 0/20 |
| 11 | 53/60 | 1/60 | 4/60 | 1/60 | 0/60 |
| 12 | 11/17 | 0/17 | 3/17 | 2/17 | 0/17 |
| Total | 97/173 | 6/173 | 21/173 | 16/173 | 3/173 |

Table 15.
Number of HFRS, scrub typhus, murine typhus and spotted fever diagnosed serologically among clinically suspect HFRS patients among US Army soldiers at The Institute for Viral Diseases, Korea University in Korea, 1988.

| | | | |
|---|---|---|---|
| Total no. of HFRS / Total no. of serum tested [1] | = | 6 / 55 | (11%) |
| Total no. of scrub typhus / Total no. of serum tested | = | 0 / 55 | (0%) |
| Total no. of murine typhus / Total no. of serum tested | = | 2 / 55 | (4%) |
| Total no. of spotted fever / Total no. of serum tested | = | 8 / 55 | (15%) |
| Total no. of leptospirosis / Total no. of serum tested | = | 2 / 55 | (4%) |
| Total no. of unknown sera / Total no. of serum tested | = | 37 / 55 | (67%) |

[1] No. of confirmed patient serologically / No. of serum from suspect HFRS patient tested

Table 16.
Number of confirmed hospitalized cases of HFRS, scrub typhus, murine typhus, spotted fever and leptospirosis by month among US Army soldiers at The Institute for Viral Diseases, Korea University in Korea, 1988.

| Month | HFRS | scrub typhus | murine typhus | spotted fever | leptospirosis |
|---|---|---|---|---|---|
| 1 | 0/3 | 0/3 | 1/3 | 1/3 | 0/3 |
| 2 | 0/0 | 0/0 | 0/0 | 0/0 | 0/0 |
| 3 | 0/6 | 0/6 | 0/6 | 0/6 | 0/4 |
| 4 | 0/4 | 0/4 | 0/4 | 0/4 | 0/4 |
| 5 | 0/2 | 0/2 | 0/2 | 1/2 | 0/2 |
| 6 | 0/5 | 0/5 | 0/5 | 1/5 | 0/5 |
| 7 | 0/2 | 0/2 | 0/2 | 1/2 | 0/2 |
| 8 | 0/2 | 0/2 | 0/2 | 0/2 | 0/2 |
| 9 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| 10 | 2/9 | 0/9 | 1/9 | 1/9 | 0/9 |
| 11 | 3/12 | 0/12 | 0/12 | 1/12 | 0/12 |
| 12 | 1/9 | 0/9 | 0/9 | 2/9 | 2/9 |
| Total | 6/55 | 0/55 | 2/55 | 8/55 | 2/55 |

cheongnamdo and Kyungsangnam-do. Of 427 murine typhus patients, 274 were male and 153 were female as shown in Table 12. More than 95% of the total patients were adult and only 1 case was confirmed under the age of 10 as shown in table 6. A large outbreak of spotted fever group of rickettsiosis was also demonstrated for the first time in Korea as shown in Tables 2,6,10 and 12. Among 311 civilian spotted fever patients, 203 were male and 108 were female. An epidemic of spotted fever occurred in October and November about the epidemic season of HFRS and spotted fever also occurred in every month of the year as shown in Table 12. Almost all of the patients were adults and more then 80% of spotted fever patients were distributed in northern parts of South Korea as shown in Table 10. Thirty-seven cases of leptospirosis were diagnosed serologically among 1,389 suspect HFRS patients as shown in Tables 2,11 and 12. Many cases of leptospirosis were found in Seoul and Kyunggido and occurred in late summer. In the Korean Army, HFRS is a major military problem and murine typhus and spotted fever are next as shown in Tables 13 and 14. In U.S. Army in Korea, HFRS and spotted fever are important infections diseases and murine typhus and leptospirosis are next as shown in Tables 15 and 16.

3. Seroepidemiologic survey of Apodemus agrarius collected in Jejudo against Hantaan virus and R. tsutsugamushi in 1988.

Sera from wild Apodemus agrarius captured in Hallim, Jejudo, a known non-endemic island of HFRS in Korea, were examined against Hantaan virus and R. tsutsugamushi. Results of a serologic study to showed that all of 98 Apodemus mice were negative to Hantaviruses but 11% of 98 Apodemus mice were seropositive against R. tsutsugamushi as shown in Table 17. This is the first report that Apodemus mice in Jejudo are reservoir hosts of Scrub typhus as in the mainland of South Korea.

Table 17.
Survey of Apodemus agrarius, the reservoir host of acute hemorrhagic diseases, collected in Jejudo in Korea, 1988.

| Location and date of collection | No. antigen and antibody positive against | | |
|---|---|---|---|
| | Hantaan virus | | R. tsutsugamushi |
| | Antigen | Antibody | Antibody |
| Jejudo, Hallim Oct.14-20 | 0/35 [1] | 0/35 | 1/35(3%) |
| Jejudo, Hallim Oct.24-29 | 0/28 | 0/28 | 10/28(36%) |
| Total | 0/63 | 0/63 | 11/63(18%) |

[1] No. of positive/no. of mice examined

4. Identification of Siberian tick typhus in Korea

Until we demonstrated the evidence of existence of spotted fever patients in South Korea in 1987, it was not known that such disease exists in Korea. Routine serologic screening for spotted fever was started in 1988 with sera from suspect HFRS patients. As shown in Table 18, twenty-one Siberian tick typhus patients were confirmed serologically among civilian suspect HFRS patients for the first time in Korea.

B. Isolation of Hantaan virus from Apodemus agrarius caught in Yecheon, Kyungsangbuk-do in 1988.

Six strains of Hantaan virus were isolated in Vero E6 cells from lungs of Apodemus agrarius captured in surrounding areas of Yecheon Air Base where the main U.S. Marine Air Force in Korea is stationed. One strain of Seoul virus was also isolated in Vero E6 cells from lungs of R. norvegicus caught in urban areas of Kunsan city, a port city in west coast of South Korea. These viruses were Hantaan and Seoul virus by PRNT and monoclonal antibody assay. One strain of Reovirus was

Table 18.
Siberian tick typhus patient among suspect-HFRS patients in Korea, 1988.

| Code no. of serum | Sex/Age | Address | Days after onset | Hospital | Antibody titer against the disease (Siberian T.T.) IgG | IgM |
|---|---|---|---|---|---|---|
| KHF88-11 | M/24 | Ansan, Kyounggi | 6/5/86 (d-2) | Kuro Hosp. Korea Univ. | 64 | 64 |
| KHF88-102 | M/34 | Yongsan, Seoul | 1/4/88 (d-31) | Kuro Hosp. Korea Univ. | 128 | 512 |
| KHF88-105 | F/47 | Yeoju, Kyounggi | 1/15/88 (d-20) | Yeoju Hosp. Korea Univ. | 64 | 64 |
| KHF88-138 | M/35 | Kuro, Seoul | 2/11/88 (d-4) | Kuro Hosp. Korea Univ. | 64 | 64 |
| KHF88-155 | M/46 | Kwanak, Seoul | 2/3/88 (d-20) | Kuro Hosp. Korea Univ. | 128 | - |
| KHF88-168 | F/63 | Seongdong, Seoul | 2/25/88 (d-7) | Handae Hosp. Hanyang Univ. | 256 | - |
| KHF88-221 | M/21 | Kangnam, Seoul | 3/22/88 (d-7) | Paik Hosp.Seoul Injae Univ. | 64 | 64 |
| KHF88-266 | M/59 | Kangwha, Seoul | 4/20/88 (d-7) | Handae Hosp. Hanyang Univ. | 128 | 256 |
| KHF88-270 | M/27 | Namyangju, Kyounggi | 4/24/88 (d-4) | Kyomunri Hosp. Kyounggido | 64 | 64 |
| KHF88-298 | F/28 | Yeongdeungpo,Seoul | 4/20/88 (d-15) | Samil Hosp. Seoul | 64 | 128 |
| KHF88-299 | F/52 | Jungku, Incheon | 5/4/88 (d-2) | Gil Hosp. Incheon | 64 | 128 |
| KHF88-397 | F/24 | Seocho, Seoul | 6/3/88 (d-4) | Yongsan Hosp. Jungang Univ. | 64 | 256 |
| KHF88-408 | M/50 | Seojang, Chungnam | 6/8/88 (d-5) | Yongsan Hosp. Jungang Univ. | 128 | 64 |
| KHF88-435 | F/20 | Emseong, Chungbuk | 6/10/88 (d-7) | Handae Hosp. Hanyang Univ. | 128 | 64 |
| KHF88-456-1 | F/24 | Seodaemoon, Seoul | 6/28/88 (d-4) | Sevrance Hosp. Yeonsei Univ. | 128 | 256 |
| KHF88-456-2 | | | 8/20/88 (d-52) | | 256 | 256 |
| KHF88-495 | F/51 | Kuro, Seoul | 4/14/88 3 month | Kuro Hosp. Korea Univ. | 512 | 64 |
| KHF88-503 | F/27 | Wonju, Kangwon | 7/11/88 (d-5) | Haewha Hosp. Korea Univ. | 256 | 128 |
| KHF88-505 | F/53 | Enpyung, Seoul | 7/18/88 (d-2) | Sevrance Hosp. Yeonsei Univ. | 128 | 64 |
| KHF88-523 | F/27 | Kwanak, Seoul | 7/20/88 (d-3) | Kuro Hosp. Korea Univ. | 64 | 256 |
| KHF88-532 | M/31 | Seongdong, Seoul | 7/22/88 (d-2) | Paik Hosp.Seoul Injae Univ. | 128 | 256 |
| KHF88-559 | F/71 | Wonseong, Kangwon | 8/8/88 (d-2) | Wonju Hosp. Kangwon | 128 | - |

Table 19.
Isolation of Hantavirus and reovirus in Vero E6 cell culture from lungs of rodent collected in the endemic areas of HFRS and scrub typhus in Korea in 1987-1988.

| No. | Code no. of virus | Date of collection | Detector system | Name of virus |
|---|---|---|---|---|
| 1 | Yecheon Apo/ 88-122 (lungs) | 06/09/88 | Vero E6 (passage 3) | Hantaan |
| 2 | Yeoncheon Apo/ 88-197 (lungs) | 09/23/88 | Vero E6 (passage 3) | Hantaan |
| 3 | Chinhae Apo/ 87-494 (lungs) | 12/11/87 | Vero E6 | Hantaan |
| 4 | Chinhae Apo/ 87-496 (lungs) | 12/11/87 | Vero E6 | Hantaan |
| 5 | Chinhae Apo/ 87-502 (lungs) | 12/11/87 | Vero E6 | Hantaan |
| 6 | Chinhae Apo/ 87-526 (lungs) | 12/11/87 | Vero E6 (passage 3) | Hantaan |
| 7 | Kunsan HR/ 86-25 (lungs) | 07/19/88 | Vero E6 (passage 3) | Seoul |
| 8 | Yeoncheon Apo/ 88-187 (lungs) | 09/23/88 | Vero E6 ++ CPE(d-7) | Reovirus |

isolated in Vero E6 cells from lungs of Apodemus agrarius captured in Yecheon. The reovirus showed cytopathic effect to Vero E6 cells and it was identified by IFAT using standard anti-reopolyvalent rabbit serum from NIH, USPHS. The details of Hantaan, Seoul and reovirus isolated from rodents in 1987-1988 are shown in the table 19.

C. HFRS and isolation of Hantavirus in Sri Lanka.

The collaborative study on Hantavirus infection in Sri Lanka between MRI Colombo, and the WHO Collaborative Centre for HFRS, Seoul was started in 1987 and the principal investigator visited Sri Lanka in 1988 to confirm the patients and survey rodents in the areas where HFRS patients had occurred in the different parts of Sri Lanka.

1. Seroepidemiological survey of Hantavirus infection among man and rodent.

Wild urban rats were trapped from the Colombo harbour. The rats, mainly R. norvegicus, were bled and the serum separated and stored at -20 C until they were sent to Seoul. Sera from 140 patients with suspected leptospirosis, hepatitis, dengue and nephritis were also sent to Seoul. The serological testing against Hantaviruses was done at the WHO Collaborating Centre for HFRS by immunofluorescent antibody (IFA) technique, the Elisa test and plaque reduction neutralization (PRN) test.

Table 20.
Seroepidemiological survey of Hantavirus infection among man and rodent in Sri Lanka.

(Percentages in parentheses)

| | No. of IF antibody positive/No. of serum tested | |
|---|---|---|
| | Human | Urban rats |
| Colombo | 11/140 (7.9%)* | 13/196 (13.5%) |

* Four out of 11 seropositives were HFRS patients.

Table 21.
Antibody titres of human sera against Hantaviruses from non-leptospirosis, NA-NB hepatitis, non-dengue and acute nephritis patients in Sri Lanka, 1986-1987.

| No. | Code no. of serum | IF antibody titer | | | ELISA antibody titer | | PRN antibody titer | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Hantaan | | | |
| | | Hantaan | Seoul | Puumala | IgG | IgM | Hantaan | Seoul |
| 1. | M861272 | 64 | 64 | - | n.t. | n.t. | n.t. | n.t. |
| 2. | M861321 | 128 | 128 | - | n.t. | n.t. | 40 | 40 |
| 3. | M861144 | 32 | 64 | - | n.t. | n.t. | n.t. | n.t. |
| 4. | S875 | 64 | 64 | - | n.t. | n.t. | n.t. | n.t. |
| 5. | S879-1 | 256 | 256 | 16 | n.t. | n.t. | 400 | 400 |
| | S879-2 | 512 | 1024 | 16 | n.t. | n.t. | 400 | 400 |
| 6. | S8716 | 64 | 64 | - | n.t. | n.t. | 40 | 40 |
| 7. | S8717 | 256 | 512 | 16 | n.t. | n.t. | 200 | 400 |
| 8. | S8754 | 1024 | 2048 | 256 | 12800 | 204800 | 80 | 80 |
| 9. | S8774 | 64 | 128 | 16 | 12800 | - | 20 | 20 |
| 10. | S87101 | 32 | 64 | - | 3200 | - | 40 | 40 |
| 11. | S87109 | 32 | 32 | - | 3200 | - | 20 | 20 |

$$\frac{\text{Total No. of positive serum}}{\text{Total No. of serum tested}} = \frac{11}{140} \text{ (7.9\%)}$$

The occurrence of Hantavirus infection among human patients and rats from the Colombo harbour are given in Table 20. Eleven (8 percent) out of 140 patients were IF antibody-positive against Hantaan virus. The details of the antibody titres by IFAT, Elisa and PRNT in these positive cases are shown in Table 21. Four patients, Nos. 2,5,7 and 8 had very high antibody titres suggestive of recent infections. In the case of patient No. 8 who had died of the illness, this is confirmed by the high titre of IgM antibody. Of the 5 patients that were tested by PRNT, 3 showed antibody, but an unusual feature was that they all had equal titres against both Hantaan and Seoul viruses. Thirteen (14 per cent) out of 196 urban rats were antibody positive against Hantaan virus; the details of antibody titres are shown in Table 22. All of the positive rats had very high antibody titres against Seoul virus and PRNT showed that rats were infected with Seoul or Seoul related virus.

Table 22.
Antibody titres of sera against Hantaviruses from urban rats captured in Colombo harbour, Sri Lanka, in 1984 and 1987.

| Code no. of serum | IF antibody titre | | | PRN antibody titre | |
|---|---|---|---|---|---|
| | Hantaan | Seoul | Puumala | Hantaan | Seoul |
| R-1 | 32 | 256 | - | 40 | 40 |
| R-2 | 16 | 64 | - | n.t. | n.t. |
| R-45 | 16 | 128 | - | 40 | 40 |
| R-873 | 64 | 256 | - | n.t. | n.t. |
| R-874 | 64 | 128 | - | n.t. | n.t. |
| R-875 | 1024 | 1024 | 256 | 80 | 1280 |
| R-876 | 1024 | 2048 | 256 | 80 | 1280 |
| R-877 | 512 | 1024 | 64 | 80 | 1280 |
| R-879 | 32 | n.t. | - | n.t. | n.t. |
| R-8713 | 64 | n.t. | 64 | n.t. | n.t. |
| R-8715 | 64 | n.t. | 32 | n.t. | n.t. |
| R-8718 | 64 | n.t. | 16 | n.t. | n.t. |
| R-8727 | 32 | n.t. | - | n.t. | n.t. |

69 rats sera were collected in 1984 and 1985.
27 rats sera were collected in 1987.

$$\frac{\text{Total No. of positive serum}}{\text{Total No. of serum tested}} = \frac{13}{96} \quad (14\ \%)$$

2. Clinical features of human patients positive for Hantavirus antibody.

Clinical features of the patients were very diverse and hemorrhagic manifestations are milder than classic types of HFRS. Clinical diagnosis of the patients were leptospirosis and hepatitis. The patient who died of the illness with meningoencephalitis is noteworthy since this is the first case with typical meningitis symptoms. Details of HFRS patients in Sri Lanka are as follows.

| Case no. | Age/ sex | Antibody titre | Clinical diagnosis | Clinical features |
|---|---|---|---|---|
| 1 | 20/M | 1024 | leptospi-rosis | Fever, myalgia, cough, conjunctival injection |
| 2 | 19/M | 512 | leptospi-rosis | Fever, chills, vigors, headache, myalgia, icterivs, conjunctival injection, abdominal tenderness, hepatomegaly, dark-coloured urine, dysuria |
| 3 | 1/F | 128 | Viral | Fever, nausea, jaundice, hepatitis scabies, hepatomegaly |
| 4 | 30/M | 1024 | Meningo-encepha-litis | Fever, chills, headache, stiff neck, myalgia, conjunctival infection, back pain, dysuria, facial palsy (died 6 day) |

3. Isolation of a Hantavirus from urban rat caught in Colombo harbour.

A Hantavirus was isolated from the lungs of R. norvegicus trapped in Colombo, 1987 in S.D. rats and Vero E6 cells. The characteristics of the virus compare with other known serotypes of Hantavirus is in Table 23. According to monoclonal antibody assay, the virus is closely related to prototype Seoul virus but distinct from Seoul virus antigenically. The pathogenicity of this virus remains to be studied.

Table 23.
Comparative titration of monoclonal antibodies against known Hantaviruses and a virus isolated from R. norvegicus caught in Colombo harbour, Sri Lanka, in 1987.

| Virus and strain | Monoclonal antibodies | | | | KHF serum 85-26-1 | NE serum 85-802 |
|---|---|---|---|---|---|---|
| | BD01-BB08 | HC02-BE08 | FD03-AA11 | FD03-AF03 | | |
| Hantaan virus 76-118 | 4096 | 16 | 16 | 16 | 4096 | 16 |
| Seoul virus 80/39 | 16 | 4096 | 64 | 64 | 4096 | 256 |
| Puumala virus #2 | 16 | 16 | 16 | 16 | 64 | 4096 |
| Prospect Hill virus | 16 | 16 | 16 | 16 | 256 | 1024 |
| Leakey virus | 16 | 16 | 16 | 16 | 64 | 4096 |
| Hong Kong R-19 | 16 | 256 | 1024 | 256 | 4096 | 256 |
| Singapore R-36 | 16 | 4096 | 256 | 256 | 8192 | 1024 |
| Sri Lanka R-1315 | 16 | 4096 | 16 | 16 | 4096 | 64 |

4. Ecology of HFRS in Sri Lanka.

(1) Many of the cases occurred in rural areas in Sri Lanka where house rats and field rodents co-exist. It is very difficult to speculate on the reservoir host of HFRS at the moment in Sri Lanka before serological study of rodents in the endemic areas are done.
(2) There are four species of rodent in Sri Lanka; house rat, house mouse, gerbil and Indian bandicoot. The rodents live in and around housing areas.
(3) Three patients among the four cases of HFRS had histories of ground work, such as construction of house, work in paddy field, gem digging and sleeping in the bush. We found many burrows of rodents in the areas where patients had worked before the illness.
(4) Sri Lanka is a fertile tropical island with about 25,000 sq miles and 16 million population. The island is rich in various kinds of foods and fruits, and dense population of rodents are found. Ships from various parts of the world, including Korea, China, USSR, Japan and European countries, visit Colombo and other harbours.

## DISCUSSION

The 367 cases of HFRS represent only serologically confirmed hospitalized patients at our Institute in 1988. Sera from suspect HFRS patients came from limited hospitals in and nearby cities of Seoul, therefore, the real total no. of HFRS in entire South Korea should be at least three times more than no. of patients in table 1 because we might have examined only one third of HFRS cases according to the distribution of civilian population and HFRS patients occur all over the South Korea.

It could be estimated that there are at least 2,000 cases of HFRS patient in S. Korea every year if serologic diagnostic capabilities are available at the endemic areas of S. Korea where we could not cover the areas to make serodiagnosis. It is interesting to learn that the no. of HFRS patient in urban areas of large cities is increasing recently and many cases occur in late fall from October to December, the same epidemic season of HFRS in the rural endemic areas of Korea. About 90% of total patients were confirmed in 4 Provinces located in northern parts of S. Korea as shown in table 4 but it might not mean that the Provinces are more heavily infected foci of HFRS than other Provinces since other Provinces are far from Seoul and it is very difficult to send sera from the suspect patients at acute stage of illness to our Institute for serologic diagnosis of the disease. All of the hospitals in endemic rural areas of Korea are incapable of making a serologic diagnosis of HFRS although patients occur all over Korea except Jeju island. Distribution

of HFRS patient in Seoul is in all districts and every district had several cases of HFRS evey year. It remains to be studied the risk factors and virulence of Seoul virus strains where about 10 million people are living and more than 10% of urban rats population is infected with Seoul virus (33).
There is a large epidemic peak of HFRS in late fall and a minor peak in May-July every year and epidemics occur among soldiers stationed in and near DMZ between South and North Korea. There were only 6 HFRS out of 55 suspect HFRS patients among about 40,000 U.S. soldiers stationed in Korea.

Recently, it has been shown that the clinical complex of acute hemorrhagic diseases in late summer and fall in Korea since 1982, includes HFRS, leptospirosis and rickettsioses (40). A large outbreak of scrub typhus was confirmed from August to November and the no. of patients was 114 among 1,389 suspect HFRS patients. There were only 37 cases of leptospirosis in this year.

We have reported the evidence for the existence of murine typhus and unknown rickettsiosis in Korea in 1988 Annual Report, and in 1989. We were able to confirm serologically many cases of murine typhus and spotted fever patients for the first time in Korea. It was surprising to learn that there were 448 murine typhus and 327 suspect spotted fever patients as shown in table 2. Among 327 seropositive patients against R. sibrica, 21 patients were confirmed serologically as Siberian tick typhus as shown in table 18. Still 7-20% of suspect total HFRS patient remains to be answered and we are trying to find the cause of the unknown fever since we have the serologic evidence of existence of Colorado tick fever like illness in Korea. Collaborative study to search the causative agents of unknown fever among suspect hemorrhagic diseases between USAMRU/Korea and our Institute is in progress in Seoul. It is also planned to isolate local strains of R. typhi and R. siberica from wild rodents and their ectoparasites in the near future.

Recent studies have demonstrated a near global distribution of Seoul virus among urban rats and the presence of this or other Hantaviruses among several different species and genera of small mammals (18-23). Clearly the genus Hantavirus (17) is widely distributed and maintained in a variety of different ecological settings. The degree to which Hantaviruses cause human disease, especially in areas where HFRS has not been traditionally recognized, is presently unknown. As the WHO collaborating Centre for research on HFRS, we provided serological diagnosis for suspect HFRS in sera from throughout the world. In addition, we have collaborated with a number of investigators conducting small mammal surveys for evidence of Hantavirus infection and isolation of strains from urban rats. Results of these preliminary studies indicate that human disease due to Hantavirus is present in several areas where HFRS had not been previously diagnosed.

We demonstrated, for the first time, serological evidence of human infection with Seoul virus in the general population of Sri Lanka.

It is very important to know that the clinical features of HFRS patients in Sri Lanka are very diverse and hemorrhagic manifestations are milder than the classic types of HFRS and that the clinical diagnoses of the patients were leptospirosis, hepatitis and meningoencephalitis. Furthermore, the Seoul virus-like virus isolated from rats in Colombo is antigenically distinct from the prototype strain of Seoul virus by monoclonal assays. It is also worthy to mention the PNR antibody titers of sera from 5 HFRS patients because the antibody titers were almost same against Hantaan and Seoul virus and this might mean that the virus in Sri Lanka is antigenically different from Seoul virus 80/39.

The impact of results of the HFRS study in Sri Lanka to clinicians in many parts of the world where HFRS is not known to exist previously is great because some of the undiagnosed unknown hemorrhagic fever patients among suspect known hemorrhagic fevers, leptospirosis, nephritis and hepatitis are HFRS caused by Seoul or Seoul-like virus. A simple rapid serologic test for HFRS that can be done at local hospitals in the endemic areas is urgently needed for not only the above reasons but also screening against Hantavirus infection in laboratory colonized animals (42-44). IF, ELISA and PRNT are very sensitive and useful diagnostic test for Hantavirus infection but require expensive requipment and techniques.

Recently, we have been working to develop a rapid simple diagnostic test with high density silicon particles for HFRS and our limited study shows promising results.

## CONCLUSION

1. There were 367 confirmed HFRS cases among 1,389 suspect HFRS patients in Korea in 1988 and, 97 and 6 of them were ROK Army and US Army soldiers, respectively.
2. There were 114 cases of scrub typhus among 1,389 suspect HFRS patients and 6 of them were ROK Army soldiers in Korea in 1988.
3. Large outbreaks of murine typhus and spotted fever were documented serologically for the first time in Korea.
4. Outbreaks of murine typhus, spotted fever and scrub typhus were observed about the time of the epidemic season of HFRS in Korea.
5. Six strains of Hantaan virus from Apodemus agrarius and one strain of Seoul virus from R. norvegicus, and one strain of reovirus from Apodemus agrarius were isolated in Vero E6 cell cultures.
6. The recent studies of HFRS in Sri Lanka indicate that this severe disease is prevalent almost everywhere although documented cases are limited and HFRS was misdiagnosed clinically as leptospirosis, hepatitis and meningitis.
7. It is noteworthy that a HFRS patient had meningoencephalitis symptoms-clinical features that were completely different from known clinical symptoms of HFRS. Therefore, it could be speculated that clinical features of HFRS patients infected with Hantaan-related viruses in tropical areas where this disease is not known to exist may be more diverse than the classic forms of HFRS in the endemic areas.
8. All the confirmed cases of HFRS in Sri Lanka occurred in the rural areas where field rats and house rats co-exist in and nearby housing areas. Therefore, it is difficult to say what species of rodent is the reservoir host of Hantavirus in Sri Lanka until a seroepidemiological survey of the rodents in done. This is the first report of four HFRS patients documented serologically and clinically in Sri Lanka.
9. A Hantavirus was isolated from the lungs of R. norvegicus caught in the Colombo harbour in 1987. The antigenicity of this virus is closely related to Seoul virus and pathogenicity of the new isolate to man remain to be studied.

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